Search Strategy

FILE 'USPATFULL' ENTERED AT 09:58:04 ON 12 AUG 2002

		E	WHITCOMB JEANETTE/IN
L1	4	S	E4-E5
L2	17619	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L3	6378	S	L2 AND (REVERSE TRANSCRIPTASE OR RT)
L4	368	S	L3 AND (NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR? OR NN
L5	286	S	L4 AND (RESIST? OR MUTANT? OR DRUG-RESISTAN?)
L6	154	S	L5 AND (DELAVIRDINE AND NEVIRAPINE)
L7	11	S	L6 AND (RESIST?/CLM OR MUTANT?/CLM)

FILE 'WPIDS' ENTERED AT 10:13:16 ON 12 AUG 2002

		E	WHITCOMB J/IN
L8	6	S	E3
L9	12516	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L10	775	S	L9 AND (RT OR REVERSE TRANSCRIPTASE)
L11	44	S	L10 AND (NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBITOR? OR N
L12	19	S	L11 AND (RESIST? OR MUTANT? OR SENSITIV?)

FILE 'MEDLINE' ENTERED AT 10:16:03 ON 12 AUG 2002

		E	WHITCOMB J/AU
L13	27	S	E3 OR E11 OR E12

FILE 'MEDLINE' ENTERED AT 12:01:33 ON 12 AUG 2002

L1	119158	S	(HIV OR HUMAN IMMUNODEFICIENCY VIRUS)
L2	7841	S	L1 AND (RT OR REVERSE TRANSCRIPTASE)
L3	762	S	L2 AND (NNRTI? OR NON-NUCLEOSIDE REVERSE TRANSCRIPTASE INHIBI
L4	414	S	L3 AND (MUTANT? OR SENSITIVIT? OR RESIST?)
L5	263	S	L4 AND (DRUG-RESIST? OR DRUG-SENSITIV?)
L6	105	S	L5 AND (DELAVIRIDINE OR NEVIRAPINE OR EFAVIRENZ)
L7	45	S	L5 AND DELAVIRDINE
L8	29	S	L7 AND NEVIRAPINE
L9	38	S	L5 AND (DP-266 OR SUSTIVA OR EFAVIRENZ)
		E	DE CLERCQ E/AU
L10	1261	S	E3 OR E4
L11	104	S	L10 AND (DRUG-RESISTAN? OR DRUG-SENSITIV?)
L12	71	S	L11 AND (HIV OR HUMAN IMMUNODEFICIENCY VIRUS)

L1 ANSWER 1 OF 4 USPATFULL
2002:178734 Means and methods for monitoring non-nucleoside reverse transcriptase inhibitor antiretroviral therapy and guiding therapeutic decisions in the treatment of HIV/AIDS.
Whitcomb, Jeannette, San Mateo, CA, UNITED STATES
Parkin, Neil T., Belmont, CA, UNITED STATES
Heilek-Snyder, Gabrielle, Mountain View, CA, UNITED STATES
US 2002094522 A1 20020718
APPLICATION: US 2001-953508 A1 20010914 (9)
PRIORITY: US 2000-231886P 20000915 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to antiviral drug susceptibility and resistance tests to be used in identifying effective drug regimens for the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and further relates to the means and methods of monitoring the clinical progression of HIV infection and its response to antiretroviral therapy, particularly non-nucleoside reverse transcriptase inhibitor therapy using phenotypic susceptibility assays or genotypic assays.

L1 ANSWER 2 OF 4 USPATFULL
2002:66848 Means and methods for monitoring antiretroviral therapy and guiding therapeutic decisions in the treatment of HIV/AIDS.
Whitcomb, Jeannette, San Mateo, CA, UNITED STATES
US 2002037500 A1 20020328
APPLICATION: US 2001-881033 A1 20010612 (9)
PRIORITY: US 2000-211245P 20000612 (60)
DOCUMENT TYPE: Utility; APPLICATION.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB This invention relates to antiviral drug susceptibility and resistance tests to be used in identifying effective drug regimens for the treatment of human immunodeficiency virus (HIV) infection and acquired immunodeficiency syndrome (AIDS) and further relates to the means and methods of monitoring the clinical progression of HIV infection and its response to antiretroviral therapy, particularly nucleoside reverse transcriptase inhibitor therapy using phenotypic susceptibility assays or genotypic assays.

L6 ANSWER 133 OF 154 USPATFULL
2001:59601 Method of managing the chemotherapy of patients who are HIV positive based on the phenotypic drug sensitivity of human HIV strains.
de Bethune, Marie-Pierre, Everberg, Belgium
Hertogs, Kurt, Antwerp, Belgium
Pauwels, Rudi, Weerde, Belgium
Virco N.V., Mechelen, Belgium (non-U.S. corporation)
US 6221578 B1 20010424
WO 9727480 19970731
APPLICATION: US 1998-117217 19980724 (9)
WO 1997-IB71 19970124 19980724 PCT 371 date 19980724 PCT 102(e) date
PRIORITY: EP 1996-200175 19960126
DOCUMENT TYPE: Utility; Granted.
CAS INDEXING IS AVAILABLE FOR THIS PATENT.

AB The present invention is drawn to A method of managing HIV chemotherapy of patients who are HIV positive, which comprises transfecting a cell line susceptible to infection by HIV with a sequence from the pol gene of HIV, which sequence encodes a

desired target enzyme, obtained by isolating viral RNA from a sample of a biological material from a patient and reverse transcribing the desired region of the pol gene, and a HIV-DNA construct from which the sequence has been deleted, culturing the transfected cells so as to create a stock of chimeric viruses providing an indication of the resistance profile of the circulating virus, assessing the phenotypic sensitivity of the chimeric viruses to an inhibitor of the enzyme encoded by the pol gene of HIV and assigning a value thereto, constructing a data set comprising the value for chimeric virus sensitivity and the corresponding value for a chimeric wild-type strain of HIV, repeating the sensitivity assessment for at least two further inhibitors and thereby constructing at least three such data sets in total, representing the data sets in two dimensional or three dimensional graphical form such that the difference between the chimeric and wild-type sensitivities in the case of each data set provides a visual measure of the resistance of the chimeric stock to treatment by the inhibitor in question, and selecting the optimum inhibitor(s) on the basis of the graphical representation of the resistance so measured.

CLM What is claimed is:

1. A method of managing HIV chemotherapy of patients who are HIV positive, which comprises transfecting a cell line susceptible to infection by HIV with a sequence from the pol gene of HIV, which sequence encodes a desired target enzyme, obtained by isolating viral RNA from a sample of a biological material from a patient and reverse transcribing the desired region of said pol gene, and a HIV-DNA construct that lacks a sequence encoding said desired target enzyme, culturing said transfected cells so as to create a stock of chimeric viruses, assessing the phenotypic sensitivity of said chimeric viruses to an inhibitor of said enzyme encoded by the pol gene of HIV and assigning a value thereto, constructing a data set comprising said value for chimeric virus sensitivity and the corresponding value for a chimeric wild-type strain of HIV, repeating the sensitivity assessment for at least two further inhibitors and thereby constructing at least three such data sets in total, representing said data sets in two dimensional or three dimensional graphical form such that the difference between the chimeric and wild-type sensitivities in the case of each data set provides a visual measure of the resistance of the chimeric stock to treatment by the inhibitor in question, and selecting the optimum inhibitor(s) on the basis of the graphical representation of the resistance so measured.

2. A method of managing HIV chemotherapy according to claim 1, wherein the data sets are represented on a polygonal or quasi-circular graph comprising: (a) a plurality of normalised axes extending radially from an origin, each axis corresponding to one data set or inhibitor or combination thereof; (b) the axes being normalised such that the sensitivity values for wild-type HIV for the various inhibitors are equal on each axis, the data points for wild-type HIV being optionally represented and connected to form a regular polygon whose vertices lie on the axes and whose center is defined by the origin; (c) on each axis a data point representing the sensitivity value of the chimeric HIV stock against the inhibitor corresponding to said axis is plotted, the chimeric data points being optionally connected to form a regular or irregular polygon the shape of which represents the resistance of the chimeric stock to a range of inhibitors.

3. A method according to claim 2, wherein each axis has a logarithmic

scale.

4. A method according to claim 3, wherein eccentric data points in the chimeric polygon, if represented, identify inhibitors whose usefulness can be assumed to be of little or no benefit to the patient, while data points lying within, on or close outside the wild-type polygon identify inhibitors whose usefulness can be assumed to be of substantial benefit to the patient.

5. A method according to claim 1, wherein each of said three or more data sets fther comprises a value for worst-case measurable resistance for the inhibitor in question, said worst case values being represented on said graphical representations such that the data point for the chimeric stock can be compared both to wild-type and to worst-case HIV, thereby providing an assessment of the relative value of the inhibitor in a particular case.

6. A method of managing HIV chemotherapy of patients who are HIV positive, which comprises the steps of: (a) periodically assessing the phenotypic sensitivity of a patient's HIV strains according to claim 1; (b) maintaining the chemotherapy with the selected inhibitor while the patient's HIV strains remain susceptible to the selected chemotherapy; (c) selecting a different inhibitor if and when the susceptibility of the original inhibitor decreases.

7. A method according to claim 1, wherein the phenotypic sensitivity of said chimeric viruses to inhibitors of at least two enzymes encoded by the pol gene of HIV is simultaneously assessed.

8. A method of determining the phenotypic drug sensitivity of individual HIV strains in a patient to inhibitors of at least two enzymes encoded by the pol gene of HIV, which comprises, transfecting a cell line susceptible to infection by HIV with a sequence from the pol gene of HIV, which sequence encodes said enzyme, obtained by isolating viral RNA from a sample of a biological material from a patient and reverse transcribing the desired region of said pol gene, and a HIV-DNA construct that lacks a sequence encoding said desired target enzyme, culturing said transfected cells so as to create a stock of chimeric viruses, and assessing the phenotypic sensitivity of said chimeric viruses to inhibitors of said enzymes encoded by the pol gene of HIV.

9. A method according to claim 1, wherein said biological material is selected from plasma, serum or a cell-free body fluid selected from semen and vaginal fluid.

10. A method according to claim 1, wherein the biological material is whole blood to which an RNA stabiliser has been added.

11. A method according to claim 1, wherein the biological material is tissue material selected from brain tissue or lymph nodal tissue.

12. A method according to claim 8, wherein the at least two enzymes are selected from HIV RT, protease and integrase.

13. A method according to claim 1, wherein the cell line susceptible to infection by HIV is a CD4.sup.+ T-cell line.

14. A method according to claim 13, wherein the CD4.sup.+ T-cell line is the MT4 cell line or the HeLa CD4.sup.+ cell line.

15. A method according to claim 1, wherein the desired region of the patient-derived HIV pol gene is reverse transcribed using a specific downstream primer.

16. A method according to claim 15, wherein the sequence to be reverse transcribed is that coding for reverse transcriptase and protease.

17. A method according to claim 16, wherein the downstream primer is OUT3: 5'-CAT TGC TCT CCA ATT ACT GTG ATA TTT CTC ATG-3' (SEQ ID NO: 1).

18. A method according to claim 15, wherein the product of reverse transcription is amplified using a nested PCR technique.

19. A method according to claim 1, wherein the HIV-DNA construct is one from which the RT and protease genes are deleted and is the plasmid pGEMT3-.DELTA.PRT as deposited at the Belgian Coordinated Collections of Microorganisms-BCCM LMBP-Collection on Nov. 8, 1996 under the number LMBP3590.

20. A method according to claim 1, wherein the transfection is achieved by electroporation.

21. A method according to claim 1, wherein the transfection is achieved by the use of cationic lipids.

22. A method according to claim 1, wherein the phenotypic drug sensitivity of the chimeric viruses to different RT, protease and integrase inhibitors is assessed in an automated cell-based assay.

23. A method according to claim 1, wherein the phenotypic drug sensitivity of the chimeric viruses and of the wild HIV strain to one or more RT, protease or integrase inhibitor(s) is expressed as an inhibitory concentration (IC value).

24. A method according to claim 1, wherein RT inhibitors are selected from nucleoside RT inhibitors such as AZT, ddI, ddC, 3TC, d4T, non-nucleoside RT inhibitors such as loviride, nevirapine and tivirapine, protease inhibitors such as saquinavir, indinavir and ritonavir and integrase inhibitors such as caffeic acid phenylethyl ester (CAPE).

L14 ANSWER 5 OF 5 WPIDS (C) 2002 THOMSON DERWENT
AN 1997-393828 [36] WPIDS
DNN N1997-327704 DNC C1997-126633
TI Managing chemotherapy of HIV patients - by determining phenotypic drug sensitivity using cells transfected with the pol gene from a patient and a pol gene-deleted HIV-DNA construct.
DC B04 D16 S03
IN DE, BETHUNE M; HERTOGS, K; PAUWELS, R
PA (VIRC-N) VIRCO NV
CYC 43
PI **WO 9727480 A1 19970731 (199736)* EN 66p**
RW: AT BE CH DE DK ES FI FR GB GR IE IT LU MC NL PT SE
W: AU BA BG BR CA CN CZ HU IL IS JP KR MX NO NZ PL RO RU SG SI SK TR UA US
AU 9713168 A 19970820 (199749)
ZA 9700669 A 19980826 (199840) 63p
NO 9803300 A 19980925 (199848)

EP 877937 A1 19981118 (199850) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT SE
NZ 325912 A 19990128 (199910)
SK 9801002 A3 19990211 (199916)
CN 1209875 A 19990303 (199928)
CZ 9802335 A3 19990616 (199929)
HU 9902618 A2 19991228 (200010)
BR 9707204 A 19991228 (200018)
AU 717755 B 20000330 (200026)
KR 99082027 A 19991115 (200052)
MX 9806006 A1 19990401 (200055)
US 6221578 B1 20010424 (200125)
RU 2174014 C2 20010927 (200174)
US 2002042679 A1 20020411 (200227)
IL 125442 A 20020310 (200239)
EP 877937 B1 20020522 (200241) EN
R: AT BE CH DE DK ES FI FR GB GR IE IT LI LU MC NL PT RO SE SI
DE 69712731 E 20020627 (200250)

ADT WO 9727480 A1 WO 1997-IB71 19970124; AU 9713168 A AU 1997-13168 19970124; ZA 9700669 A ZA 1997-669 19970127; NO 9803300 A WO 1997-IB71 19970124, NO 1998-3300 19980716; EP 877937 A1 EP 1997-900712 19970124, WO 1997-IB71 19970124; NZ 325912 A NZ 1997-325912 19970124, WO 1997-IB71 19970124; SK 9801002 A3 WO 1997-IB71 19970124, SK 1998-1002 19970124; CN 1209875 A CN 1997-191904 19970124; CZ 9802335 A3 WO 1997-IB71 19970124, CZ 1998-2335 19970124; HU 9902618 A2 WO 1997-IB71 19970124, HU 1999-2618 19970124; BR 9707204 A BR 1997-7204 19970124, WO 1997-IB71 19970124; AU 717755 B AU 1997-13168 19970124; KR 99082027 A WO 1997-IB71 19970124, KR 1998-705747 19980725; MX 9806006 A1 MX 1998-6006 19980724; US 6221578 B1 WO 1997-IB71 19970124, US 1998-117217 19980724; RU 2174014 C2 WO 1997-IB71 19970124, RU 1998-116294 19970124; US 2002042679 A1 Div ex WO 1997-IB71 19970124, Div ex US 1998-117217 19980724, US 2000-735487 20001214; IL 125442 A IL 1997-125442 19970124; EP 877937 B1 EP 1997-900712 19970124, WO 1997-IB71 19970124; DE 69712731 E DE 1997-612731 19970124, EP 1997-900712 19970124, WO 1997-IB71 19970124

FDT AU 9713168 A Based on WO 9727480; EP 877937 A1 Based on WO 9727480; NZ 325912 A Based on WO 9727480; CZ 9802335 A3 Based on WO 9727480; HU 9902618 A2 Based on WO 9727480; BR 9707204 A Based on WO 9727480; AU 717755 B Previous Publ. AU 9713168, Based on WO 9727480; KR 99082027 A Based on WO 9727480; US 6221578 B1 Based on WO 9727480; RU 2174014 C2 Based on WO 9727480; US 2002042679 A1 Div ex US 6221578; IL 125442 A Based on WO 9727480; EP 877937 B1 Based on WO 9727480; DE 69712731 E Based on EP 877937, Based on WO 9727480

PRAI EP 1996-200175 19960126

AB **WO 9727480 A UPAB: 19970909**

A method for managing HIV chemotherapy of HIV positive patients comprises: (a) transfecting an HIV infection-susceptible cell line with an HIV pol gene sequence obtained from a patient and a HIV-DNA construct from which the sequence has been deleted; (b) culturing the transfected cells so as to create a stock of chimeric viruses; (c) assessing the phenotypic sensitivity of the chimeric viruses to an inhibitor of the HIV pol gene-encoded enzyme and assigning a value; (d) constructing a data set comprising the value for chimeric virus sensitivity and the corresponding value for a chimeric wild-type strain of HIV; (e) repeating the sensitivity assessment for at least two further inhibitors and thereby constructing at least three such data sets; (f) representing the data sets in 2-D or 3-D graphical form such that the difference between the chimeric and wild-type sensitivities in each data set provides a visual measure of the resistance of the chimeric stock to treatment by the inhibitor; and (g) selecting the optimum inhibitor(s) on the basis of the graphical representation of the resistances.

USE - The method provides phenotypic data on patient HIV strains which can be immediately used to determine whether a particular chemotherapeutic regimen should be initiated, continued or adjusted. The method in combination with the administration of the correct anti-HIV drugs should ultimately lead to better treatment, improved quality of life and improved survival of HIV infected patients.
Dwg.0/12

L13 ANSWER 1 OF 27 MEDLINE
2002413478 Document Number: 22157917. PubMed ID: 12167680.
Antiretroviral-drug resistance among patients recently infected with HIV. Little Susan J; Holte Sarah; Routy Jean-Pierre; Daar Eric S; Markowitz Marty; Collier Ann C; Koup Richard A; Mellors John W; Connick Elizabeth; Conway Brian; Kilby Michael; Wang Lei; Whitcomb Jeannette M; Hellmann Nicholas S; Richman Douglas D. (Antiviral Research Center, Department of Medicine, University of California-San Diego, San Diego 92103, USA.. slittle@ucsd.edu) . **NEW ENGLAND JOURNAL OF MEDICINE, (2002 Aug 8) 347 (6) 385-94.** Journal code: 0255562. ISSN: 1533-4406. Pub. country: United States. Language: English.

AB BACKGROUND: Among persons in North America who are newly infected with the human immunodeficiency virus (HIV), the prevalence of transmitted resistance to antiretroviral drugs has been estimated at 1 to 11 percent. METHODS: We performed a retrospective analysis of susceptibility to antiretroviral drugs before treatment and drug-resistance mutations in HIV in plasma samples from 377 subjects with primary HIV infection who had not yet received treatment and who were identified between May 1995 and June 2000 in 10 North American cities. Responses to treatment could be evaluated in 202 subjects. RESULTS: Over the five-year period, the frequency of transmitted drug resistance increased significantly. The frequency of high-level resistance to one or more drugs (indicated by a value of more than 10 for the ratio of the 50 percent inhibitory concentration [IC50] for the subject's virus to the IC50 for a drug-sensitive reference virus) increased from 3.4 percent during the period from 1995 to 1998 to 12.4 percent during the period from 1999 to 2000 (P=0.002), and the frequency of multidrug resistance increased from 1.1 percent to 6.2 percent (P=0.01). The frequency of resistance mutations detected by sequence analysis increased from 8.0 percent to 22.7 percent (P<0.001), and the frequency of multidrug resistance detected by sequence analysis increased from 3.8 percent to 10.2 percent (P=0.05). Among subjects infected with drug-resistant virus, the time to viral suppression after the initiation of antiretroviral therapy was longer (P=0.05), and the time to virologic failure was shorter (P=0.05). CONCLUSIONS: The proportion of new HIV infections that involve drug-resistant virus is increasing in North America. Initial antiretroviral therapy is more likely to fail in patients who are infected with drug-resistant virus. Testing for resistance to drugs before therapy begins is now indicated even for recently infected patients.

L13 ANSWER 2 OF 27 MEDLINE
2001572085 Document Number: 21536998. PubMed ID: 11679926. Inhibition of purified recombinant reverse transcriptase from wild-type and zidovudine-resistant clinical isolates of human immunodeficiency virus type 1 by zidovudine, stavudine, and lamivudine triphosphates. Duan C; Poticha D; Stoeckli T C; Petropoulos C J; Whitcomb J M; McHenry C S; Kuritzkes D R. (Division of Infectious Diseases, University of Colorado Health Sciences Center, Denver, CO 80262, USA.. duan_cy@yahoo.com) . JOURNAL OF INFECTIOUS DISEASES, (2001 Nov 15) 184 (10) 1336-40. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Cross-resistance between zidovudine, stavudine, and lamivudine was studied, using purified recombinant reverse transcriptase from a zidovudine-susceptible and -resistant pair of clinical isolates of human immunodeficiency virus type 1. The zidovudine-resistant isolate exhibited low-level cross-resistance to both stavudine and lamivudine in drug susceptibility assays. Enzyme from the resistant isolate demonstrated

reduced inhibition by zidovudine triphosphate and stavudine triphosphate and, to a lesser extent, lamivudine triphosphate. These findings provide additional evidence at the viral and enzyme level for cross-resistance between zidovudine and stavudine, and they suggest a possible effect of zidovudine resistance on susceptibility to lamivudine.

L13 ANSWER 3 OF 27 MEDLINE

2001351623 Document Number: 21307972. PubMed ID: 11416714. Phenotypic hypersusceptibility to non-nucleoside reverse transcriptase inhibitors in treatment-experienced HIV-infected patients: impact on virological response to efavirenz-based therapy. Shulman N; Zolopa A R; Passaro D; Shafer R W; Huang W; Katzenstein D; Israelski D M; Hellmann N; Petropoulos C; Whitcomb J. (Stanford University School of Medicine, Stanford, CA 94305, USA.) **AIDS, (2001 Jun 15) 15 (9) 1125-32**. Journal code: 8710219. ISSN: 0269-9370. Pub. country: England: United Kingdom. Language: English.

AB BACKGROUND: Enhanced susceptibility to non-nucleoside reverse transcriptase inhibitors (NNRTI) was recently described in association with increased resistance to nucleoside analogs (nucleoside reverse transcriptase inhibitors; NRTI). OBJECTIVES: To determine the prevalence of NNRTI hypersusceptibility, the genotypic correlates, and its impact on virologic response to efavirenz-based salvage therapy. METHODS: Genotype and phenotype testing was performed retrospectively on baseline isolates from 30 patients who received salvage therapy containing efavirenz. NNRTI hypersusceptibility was defined as a 50% inhibitory concentration (IC(50)) of < 0.5 that of the wild-type control. RESULTS: Eight isolates had major NNRTI mutations. Among the 22 isolates with no major NNRTI mutations, 11 (50%) were hypersusceptible to efavirenz, 10 (45%) to delavirdine, and eight (36%) to nevirapine. Among eight isolates with NNRTI mutations, NNRTI resistance was present, but at lower than expected levels. The number of NRTI mutations was correlated inversely with the fold decrease in susceptibility to efavirenz (Spearman's rho, -0.57; P = 0.005), delavirdine (rho, -0.43; P = 0.04), and nevirapine (rho, -0.69; P < 0.001). Excluding subjects with NNRTI mutations, subjects with efavirenz hypersusceptibility at baseline had significantly better virologic suppression over 24 weeks than those without efavirenz hypersusceptibility (P < 0.001). CONCLUSION: NNRTI hypersusceptibility is common in heavily treated but NNRTI naive patients and is related directly to NRTI resistance mutations. Among patients receiving efavirenz-containing regimens, NNRTI hypersusceptibility was associated with an improved virologic outcome after 24 weeks of therapy. A reversal of phenotypic resistance was seen in patients with NNRTI mutations in the presence of multiple NRTI mutations, but no obvious virologic benefit of this phenomenon was seen in this study.

L13 ANSWER 5 OF 27 MEDLINE

2001031501 Document Number: 20499048. PubMed ID: 11044070. Reduced susceptibility of human immunodeficiency virus type 1 (HIV-1) from patients with primary HIV infection to nonnucleoside reverse transcriptase inhibitors is associated with variation at novel amino acid sites. Brown A J; Precious H M; Whitcomb J M; Wong J K; Quigg M; Huang W; Daar E S; D'Aquila R T; Keiser P H; Connick E; Hellmann N S; Petropoulos C J; Richman D D; Little S J. (Centre for HIV Research, Institute of Cell, Animal and Population Biology, University of Edinburgh, Edinburgh, Scotland.. A.Leigh-Brown@ed.ac.uk) . **JOURNAL OF VIROLOGY, (2000 Nov) 74 (22) 10269-73**. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Recently, significant numbers of individuals with primary human immunodeficiency virus (HIV) infection have been found to harbor viral

strains with reduced susceptibility to antiretroviral drugs. In one study, HIV from 16% of such antiretroviral-naive individuals was shown to have a susceptibility to nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs) between 2.5- and 10-fold lower than that of a wild-type control. Mutations in the RT domain that had previously been associated with antiretroviral resistance were not shared by these strains. We have analyzed by logistic regression 46 variable amino acid sites in RT for their effect on susceptibility and have identified two novel sites influencing susceptibility to NNRTIs: amino acids 135 and 283 in RT. Eight different combinations of amino acids at these sites were observed among these patients. These combinations showed a 14-fold range in mean susceptibility to both nevirapine and delavirdine. In vitro mutagenesis of the control strain combined with a phenotypic assay confirmed the significance of amino acid variation at these sites for susceptibility to NNRTIs.

L13 ANSWER 7 OF 27 MEDLINE
2000187151 Document Number: 20187151. PubMed ID: 10722492. A novel phenotypic drug susceptibility assay for human immunodeficiency virus type 1. Petropoulos C J; Parkin N T; Limoli K L; Lie Y S; Wrin T; Huang W; Tian H; Smith D; Winslow G A; Capon D J; Whitcomb J M. (ViroLogic, Inc., South San Francisco, California 94080, USA.. cpetropoulos@virologic.com) . **ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (2000 Apr) 44 (4) 920-8.** Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Although combination antiretroviral therapy has resulted in a considerable improvement in the treatment of human immunodeficiency virus (HIV) type 1 (HIV-1) infection, the emergence of resistant virus is a significant obstacle to the effective management of HIV infection and AIDS. We have developed a novel phenotypic drug susceptibility assay that may be useful in guiding therapy and improving long-term suppression of HIV replication. Susceptibility to protease (PR) and reverse transcriptase (RT) inhibitors is measured by using resistance test vectors (RTVs) that contain a luciferase indicator gene and PR and RT sequences derived from HIV-1 in patient plasma. Cells are transfected with RTV DNA, resulting in the production of virus particles that are used to infect target cells. Since RTVs are replication defective, luciferase activity is measured following a single round of replication. The assay has been automated to increase throughput and is completed in 8 to 10 days. Test results may be useful in facilitating the selection of optimal treatment regimens for patients who have failed prior therapy or drug-naive patients infected with drug-resistant virus. In addition, the assay can be used to evaluate candidate drugs and assist in the development of new drugs that are active against resistant strains of HIV-1.

L13 ANSWER 8 OF 27 MEDLINE
2000097805 Document Number: 20097805. PubMed ID: 10634339. Drug susceptibility in HIV infection after viral rebound in patients receiving indinavir-containing regimens. Havlir D V; Hellmann N S; Petropoulos C J; Whitcomb J M; Collier A C; Hirsch M S; Tebas P; Sommadossi J P; Richman D D. (University of California, San Diego 92103, USA.. dhavlir@ucsd.edu) . JAMA, (2000 Jan 12) 283 (2) 229-34. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB CONTEXT: Loss of viral suppression in patients infected with human immunodeficiency virus (HIV), who are receiving potent antiretroviral therapy, has been attributed to outgrowth of drug-resistant virus; however, resistance patterns are not well characterized in patients whose protease inhibitor combination therapy fails afterachieving viral suppression. OBJECTIVE: To characterize drug susceptibility of virus from

HIV-infected patients who are failing to sustain suppression while taking an indinavir-containing antiretroviral regimen. DESIGN AND SETTING: Substudy of the AIDS Clinical Trials Group 343, a multicenter clinical research trial conducted between February 1997 and October 1998. PATIENTS: Twenty-six subjects who experienced rebound (HIV RNA level > or =200 copies/mL) during indinavir monotherapy (n = 9) or triple-drug therapy (indinavir, lamivudine, and zidovudine; n = 17) after initially achieving suppression while receiving all 3 drugs, and 10 control subjects who had viral suppression while receiving triple-drug therapy. MAIN OUTCOME MEASURE: Drug susceptibility, determined by a phenotypic assay and genotypic evidence of resistance assessed by nucleotide sequencing of protease and reverse transcriptase, compared among the 3 patient groups. RESULTS: Indinavir resistance was not detected in the 9 subjects with viral rebound during indinavir monotherapy or in the 17 subjects with rebound during triple-drug therapy, despite plasma HIV RNA levels ranging from 10(2) to 10(5) copies/mL. In contrast, lamivudine resistance was detected by phenotypic assay in rebound isolates from 14 of 17 subjects receiving triple-drug therapy, and genotypic analyses showed changes at codon 184 of reverse transcriptase in these 14 isolates. Mean random plasma indinavir concentrations in the 2 groups with rebound were similar to those of a control group with sustained viral suppression, although levels below 50 ng/mL were more frequent in the triple-drug group than in the control group (P = .03). CONCLUSIONS: Loss of viral suppression may be due to suboptimal antiviral potency, and selection of a predominantly indinavir-resistant virus population may be delayed for months even in the presence of ongoing indinavir therapy. The results suggest possible value in assessing strategies using drug components of failing regimens evaluated with resistance testing.

L13 ANSWER 9 OF 27 MEDLINE
1999429225 Document Number: 99429225. PubMed ID: 10501117. Reduced antiretroviral drug susceptibility among patients with primary HIV infection. Little S J; Daar E S; D'Aquila R T; Keiser P H; Connick E; Whitcomb J M; Hellmann N S; Petropoulos C J; Sutton L; Pitt J A; Rosenberg E S; Koup R A; Walker B D; Richman D D. (Department of Medicine, University of California, San Diego, USA.. slittle@ucsd.edu) . JAMA, (1999 Sep 22-29) 282 (12) 1142-9. Journal code: 7501160. ISSN: 0098-7484. Pub. country: United States. Language: English.

AB CONTEXT: The transmission of drug-resistant human immunodeficiency virus (HIV) has been documented, but the prevalence of such transmission is unknown. OBJECTIVE: To assess the spectrum and frequency of antiretroviral susceptibility among subjects with primary HIV infection. DESIGN, SETTING, AND PATIENTS: Retrospective analysis of 141 subjects identified from clinical research centers in 5 major metropolitan areas, enrolled from 1989 to 1998, with HIV seroconversion within the preceding 12 months and no more than 7 days' prior antiretroviral (ARV) therapy. MAIN OUTCOME MEASURES: Phenotypic and genotypic ARV susceptibility of HIV from plasma samples. RESULTS: The transmission of drug-resistant HIV as assessed by a greater than 10-fold reduction in ARV susceptibility to 1 or more drugs was observed in 3 (2%) of 141 subjects, including to a nonnucleoside reverse transcriptase inhibitor in 1 patient and to a nucleoside reverse transcriptase inhibitor and a protease inhibitor in 2 patients. Population-based sequence analysis of these 3 samples identified multidrug-resistance mutations in reverse transcriptase (M184V, T215Y, K219K/R) and protease (L101/V, K20R, M361, M46I, G48V, L63P, A71T, V771, V82T, 184V, L90M) in the 2 latter patient samples, along with numerous polymorphisms. A reduction in susceptibility of greater than 2.5- to 10-fold to 1 or more drugs was observed in viral isolates from 36 patients (26%). Sequence analysis of these 36 samples identified well-characterized drug resistance mutation in reverse transcriptase and protease in only 1

of these patients. CONCLUSIONS: Reductions in drug susceptibility of more than 10-fold were rare among this cohort of recently HIV-infected subjects and were distributed among each of the 3 major classes of ARV drugs tested. Reductions in susceptibility of more than 2.5- to 10-fold to certain ARV drugs of unknown clinical significance were highly prevalent among newly infected patients. Resistance testing may be warranted to monitor the frequency of drug resistance over time and to assess the potential for geographic variability.

L6 ANSWER 105 OF 105 MEDLINE
92186808 Document Number: 92186808. PubMed ID: 1372083. In vitro selection and molecular characterization of human immunodeficiency virus-1 resistant to non-nucleoside inhibitors of reverse transcriptase.
Mellors J W; Dutschman G E; Im G J; Tramontano E; Winkler S R; Cheng Y C. (Department of Internal Medicine, Yale University School of Medicine, West Haven, Connecticut.) **MOLECULAR PHARMACOLOGY, (1992 Mar) 41 (3) 446-51.** Journal code: 0035623. ISSN: 0026-895X. Pub. country: United States. Language: English.

AB Several newly discovered potent and selective non-nucleoside inhibitors of human immunodeficiency virus-1 reverse transcriptase (RT) are undergoing evaluation in clinical trials. We studied the potential for development of viral resistance to one of the prototype compounds, BI-RG-587, a dipyridodiazepinone derivative. Human immunodeficiency virus-1 resistant to **BI-RG-587** emerged after only one cycle of in vitro infection in the presence of the drug. Resistant virus was cross-resistant to the non-nucleoside tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-thione derivative R82150 but remained susceptible to 2',3'-dideoxynucleosides and phosphonoformate. Both native (virion-associated) and recombinant RT derived from resistant virus were insensitive to BI-RG-587 and R82150. Nucleotide sequence analysis of multiple drug-resistant and -sensitive recombinant RT clones identified a single predicted amino acid change common to all resistant clones (**tyrosine-181----cysteine**). These studies suggest that the viral resistance to non-nucleoside RT inhibitors may develop in vivo. This possibility should be carefully monitored in clinical trials of these compounds.

L6 ANSWER 104 OF 105 MEDLINE
93128874 Document Number: 93128874. PubMed ID: 1282792. 3'-Azido-3'-deoxythymidine resistance suppressed by a mutation conferring human immunodeficiency virus type 1 resistance to nonnucleoside reverse transcriptase inhibitors. Larder B A. (Department of Molecular Sciences, Wellcome Research Laboratories, Beckenham, Kent, United Kingdom.) **ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1992 Dec) 36 (12) 2664-9.** Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Nonnucleoside reverse transcriptase (NNRT) inhibitors (R82913; (+)-S-4,5,6,7-tetrahydro-9-chloro-5-methyl-6-(3-methyl-2-butenyl)-imidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-thione; Cl-TIBO; and BI-RG-587, **nevirapine**) were used to select resistant human immunodeficiency virus type 1 (HIV-1) variants by passage in cell cultures of wild-type or 3'-azido-3'-deoxythymidine (zidovudine; AZT)-resistant strains. Similar to other NNRT inhibitors, Cl-TIBO induced a single mutation (**Y181**

to C) in reverse transcriptase (RT) that accounted for the resistance. BI-RG-587 induced a different
→ mutation (V106-->A) in AZT resistance backgrounds. A series of viable HIV-1 variants was constructed by site-directed mutagenesis of the RT, which harbored multiple drug resistance mutations, including Y181 to C. HIV-1 that was co-resistant to NNRT inhibitors and 2',3'-dideoxyinosine resulted when a 2',3'-dideoxyinosine resistance mutation (L74 to V) was also present in RT. By contrast, however, the Y181 to C mutation in an AZT resistance background significantly suppressed resistance to AZT, while it conferred resistance to NNRT inhibitors. However, the V106-->A substitution did not cause suppression of preexisting AZT resistance. Since certain combinations of nucleoside analogs and NNRT inhibitors might result in the development of co-resistance, careful analysis of clinical isolates obtained during combination therapy will be needed to determine the potential significance of these observations.

L6 ANSWER 103 OF 105 MEDLINE
93281649 Document Number: 93281649. PubMed ID: 7685109. A mutation in reverse transcriptase of bis(heteroaryl)piperazine-resistant human immunodeficiency virus type 1 that confers increased sensitivity to other nonnucleoside inhibitors. Dueweke T J; Pushkarskaya T; Poppe S M; Swaney S M; Zhao J Q; Chen I S; Stevenson M; Tarpley W G. (Cancer and Infectious Diseases Research, Upjohn Laboratories, Kalamazoo, MI 49001.) **PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 May 15) 90 (10) 4713-7**. Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Several nonnucleoside inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) have been described, including **Nevirapine**, thiobenzimidazolone (TIBO) derivatives, pyridinone derivatives such as L-697,661, and the bis(heteroaryl)piperazines (BHAPs). HIV-1 resistant to L-697,661 or Nevirapine emerges rapidly in infected patients treated with these drugs, and the resistance is caused primarily by substitutions at amino acids 181 and 103 of RT that also confer cross resistance to the other nonnucleoside inhibitors. We describe derivation and characterization of two BHAP-resistant HIV-1 variants that differ from this pattern of cross resistance. With both variants, HIV-1 resistance to BHAP RT inhibitors was caused by a RT mutation that results in a proline-to-leucine substitution at amino acid **236 (P236L)**. Rather than conferring cross resistance to other RT inhibitors, this substitution sensitized RT 7- to 10-fold to Nevirapine, TIBO R82913, and L-697,661 without influencing sensitivity to nucleoside analogue RT inhibitors. This sensitization caused by P236L was also observed in cell culture with BHAP-resistant HIV-1. The effects of the P236L RT substitution suggest that emergence of BHAP-resistant virus in vivo could produce a viral population sensitized to inhibition by these other nonnucleoside RT inhibitors.

L6 ANSWER 101 OF 105 MEDLINE
93353611 Document Number: 93353611. PubMed ID: 7688822. Treatment of human immunodeficiency virus type 1 (HIV-1)-infected cells with combinations of HIV -1-specific inhibitors results in a different resistance pattern

than does treatment with single-drug therapy. Balzarini J; Karlsson A; Perez-Perez M J; Camarasa M J; Tarpley W G; De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) **JOURNAL OF VIROLOGY, (1993 Sep) 67 (9) 5353-9.** Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1)-infected CEM cells were treated by the HIV -1-specific inhibitors bis-heteroarylpiperazine (BHAP), 4,5,6,7-tetrahydro-5-methylimidazo[4,5,1-jk][1,4]benzodiazepin-2(1 H)-on e (TIBO) R82913, nevirapine, and the N3-methylthymine derivative of [2',5'-bis-O-(tert-butyldimethylsilyl)-beta-D-ribofuranosyl]-3'-spiro-5''-(4''-amino-1'',2''-oxathiole-2'',2''-dioxide) (TSAO-m3T), as single agents or in combination, at escalating concentrations. When used individually, the compounds led to the emergence of drug-resistant virus strains within two to five subcultivations. The resulting strains were designated HIV-1/BHAP, HIV -1/TIBO, HIV-1/Nev, and HIV-1/TSAO-m3T, respectively. The mutant viruses showed the following amino acid substitutions in their reverse transcriptase (RT): Leu-100-->Ile for HIV-1/BHAP; Lys-103-->Asn for HIV -1/TIBO; Val-106-->Ala for HIV-1/Nev; and Glu-138-->Lys for HIV-1/TSAO-m3T. Both the **Tyr-181-->Cys** and Val-106-->Ala mutations were found in another mutant emerging following treatment with **nevirapine** at escalating concentrations. The BHAP-resistant virus remained fully sensitive to the inhibitory effects of nevirapine and TSAO-m3T, whereas the TSAO-m3T-resistant virus remained fully sensitive to the inhibitory effects of nevirapine and BHAP. When different pairs of nonnucleoside RT inhibitors (i.e., BHAP plus TSAO-m3T, nevirapine plus TSAO-m3T, TIBO plus TSAO-m3T, nevirapine plus TIBO, and BHAP plus nevirapine) were used, resistant virus emerged as fast as with single-drug therapy. In all cases the **Tyr-181-->Cys** mutation appeared; the virus showed markedly reduced sensitivity to all HIV -1-specific inhibitors but retained sensitivity to 2',3'-dideoxynucleoside analogs such as zidovudine, ddC, and ddI. Our findings argue against simultaneous combination of two different nonnucleoside RT inhibitors that are unable to inhibit HIV-1 mutant strains containing the Tyr-181-->Cys mutation when administered as single drugs.

L6 ANSWER 98 OF 105 MEDLINE
94305388 Document Number: 94305388. PubMed ID: 7518271. The genetic and functional basis of HIV-1 resistance to nonnucleoside reverse transcriptase inhibitors. Emini E A; Byrnes V W; Condra J H; Schleif W A; Sardana V V. (Merck Research Laboratories, West Point, Pennsylvania.) ARCHIVES OF VIROLOGY. SUPPLEMENTUM, (1994) 9 11-7. Ref: 22. Journal code: 9214275. ISSN: 0939-1983. Pub. country: Austria. Language: English.

AB The nonnucleoside reverse transcriptase (RT) inhibitors are structurally diverse compounds that are specific inhibitors of the human immunodeficiency virus type 1 RT enzyme. The compounds are largely functionally identical and bind to a common site in the enzyme. HIV-1 variants that exhibit reduced susceptibility to these inhibitors have been derived in cell culture and, more recently, from HIV-1-infected patients undergoing experimental therapy. The variants express amino acid substitutions at RT positions that apparently interact directly

with the inhibitors. Effects of specific substitutions at these positions vary among the compounds, suggesting subtle differences in how the compounds physically interact with the enzyme.

L6 ANSWER 96 OF 105 MEDLINE
95181857 Document Number: 95181857. PubMed ID: 7533197. High-dose nevirapine: safety, pharmacokinetics, and antiviral effect in patients with human immunodeficiency virus infection. Havlir D; Cheeseman S H; McLaughlin M; Murphy R; Erice A; Spector S A; Greenough T C; Sullivan J L; Hall D; Myers M; +. (Department of Medicine, University of California, San Diego.) JOURNAL OF INFECTIOUS DISEASES, (1995 Mar) 171 (3) 537-45. Journal code: 0413675. ISSN: 0022-1899. Pub. country: United States. Language: English.

AB Nevirapine, a potent nonnucleoside reverse transcriptase inhibitor, produces a transient antiviral effect at < or = 200 mg/day due to the selection of resistant virus. To examine if higher levels of nevirapine could produce sustained antiviral activity, its safety, pharmacokinetics, and antiviral activity at 400 mg/day were studied in 21 patients. There was a rapid reduction in immune complex-dissociated p24 antigen and serum human immunodeficiency virus RNA concentration in all patients, and 8 of 10 patients had > 50% reduction at 8 weeks. Nevirapine-resistant virus was isolated from all subjects tested at 12 weeks: The mean plasma trough level (4.0 micrograms/mL [15.8 microM]) exceeded the mean IC50 of resistant virus. Rash developed in 48% of patients and was a dose-limiting toxicity factor in 6. These data suggest that clinical testing of potent antiviral compounds that select for drug-resistant virus is justified to determine if serum levels of drug sufficient to overcome resistant virus can be attained.

L6 ANSWER 91 OF 105 MEDLINE
96319790 Document Number: 96319790. PubMed ID: 8700148. Highly favorable antiviral activity and resistance profile of the novel thiocarboxanilide pentenyloxy ether derivatives UC-781 and UC-82 as inhibitors of human immunodeficiency virus type 1 replication. Balzarini J; Pelemans H; Aquaro S; Perno C F; Witvrouw M; Schols D; De Clercq E; Karlsson A. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.. jan.balzarini@rega.kuleuven.ac.be) . **MOLECULAR PHARMACOLOGY, (1996 Aug) 50 (2) 394-401.** Journal code: 0035623. ISSN: 0026-895X. Pub. country: United States. Language: English.

AB The novel human immunodeficiency virus type 1-specific thiocarboxanilide derivatives that contain either a substituted furanyl (UC-781) or thienyl (UC-82) ring linked to the thiocarboxy group and a pentenyloxyether chain linked to the 4-chlorophenyl ring in meta position show highly favorable antiviral properties. Compounds UC-781 and UC-82 discovered by scientists at Uniroyal Chemical Ltd. proved to be > or = 5-10-fold more inhibitory to wild-type human immunodeficiency virus type 1 strains (EC50 approximately 0.002 microgram/ml) than the thiocarboxanilide oxime ether UC-10 and other non-nucleoside reverse transcriptase inhibitors such as nevirapine, bis(heteroaryl)piperazine, and tetrahydroimidazo[4,5,1-jk][1,4]-benzodiazepin-2(1H)-one. In addition, the compounds were able to knock out virus replication in cell culture at concentrations that were 20-50-fold lower than those of nevirapine or bis(heteroaryl)piperazine. They were also highly efficient (EC50 < or = 0.02 microgram/ml) in suppressing the replication of mutant virus strains that

contained mutations in their reverse transcriptase that conferred resistance to other non-nucleoside reverse transcriptase inhibitors (i.e., **Tyr181 to Cys, Lys103 to Asn**, Val106 to Ala, and Leu100 to Ile). The compounds selected for virus mutants that were only marginally resistant to the thiocarboxanilides (< 10-20-fold). The antiviral activity of the compounds was only slightly affected by the presence of high concentrations of human serum, and the compounds were shown to be highly stable in the presence of human serum for at least 24 hr at room temperature.

L8 ANSWER 29 OF 29 MEDLINE
93281649 Document Number: 93281649. PubMed ID: 7685109. A mutation in reverse transcriptase of bis(heteroaryl)piperazine-resistant human immunodeficiency virus type 1 that confers increased sensitivity to other nonnucleoside inhibitors. Dueweke T J; Pushkarskaya T; Poppe S M; Swaney S M; Zhao J Q; Chen I S; Stevenson M; Tarpley W G. (Cancer and Infectious Diseases Research, Upjohn Laboratories, Kalamazoo, MI 49001.) **PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF THE UNITED STATES OF AMERICA, (1993 May 15) 90 (10) 4713-7.** Journal code: 7505876. ISSN: 0027-8424. Pub. country: United States. Language: English.

AB Several nonnucleoside inhibitors of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) have been described, including Nevirapine, thiobenzimidazolone (TIBO) derivatives, pyridinone derivatives such as L-697,661, and the **bis(heteroaryl)piperazines (BHAPs)**. HIV-1 resistant to L-697,661 or **Nevirapine** emerges rapidly in infected patients treated with these drugs, and the **resistance is caused primarily by substitutions at amino acids 181 and 103 of RT** that also confer cross resistance to the other nonnucleoside inhibitors. We describe derivation and characterization of two BHAP-resistant HIV-1 variants that differ from this pattern of cross resistance. With both variants, **HIV-1 resistance to BHAP RT inhibitors was caused by a RT mutation that results in a proline-to-leucine substitution at amino acid 236 (P236L).** Rather than conferring cross resistance to other RT inhibitors, this substitution sensitized RT 7- to 10-fold to Nevirapine, TIBO R82913, and L-697,661 without influencing sensitivity to nucleoside analogue RT inhibitors. This sensitization caused by P236L was also observed in cell culture with BHAP-resistant HIV-1. The effects of the P236L RT substitution suggest that emergence of BHAP-resistant virus in vivo could produce a viral population sensitized to inhibition by these other nonnucleoside RT inhibitors.

L8 ANSWER 24 OF 29 MEDLINE
1998296655 Document Number: 98296655. PubMed ID: 9632999. New antiretrovirals and new combinations. Havlir D V; Lange J M. (University of California, San Diego, USA.) AIDS, (1998) 12 Suppl A S165-74. Ref: 103. Journal code: 8710219. ISSN: 0269-9370. Pub. country: United States. Language: English.

AB The appearance in the clinic of two to three new antiretroviral agents yearly since 1995 has permitted unprecedented advances in HIV treatment. This remarkable pace of drug development is a testimony to an extraordinary international effort involving scientists, clinicians, governments, community activists and industry dedicated to the rapid and

safe development of novel therapies. New drugs present the opportunity to improve HIV therapy. They also create an enormous challenge to the clinician, who must constantly assimilate data on new drugs and incorporate this information into practical management strategies. Combination therapy has proven the most effective approach to treat HIV disease. The profound and sustained viral suppression achievable with combinations such as indinavir (IDV), lamivudine (3TC) and zidovudine (ZDV) have resulted in a dramatic shift in HIV treatment paradigms over the last year. The full potential of combination therapy with available drugs has yet to be realized as only a limited number of the possible combinations incorporating new drugs have been fully tested. Even drugs available for many years may have untapped potential. Didanosine (ddI) and stavudine (d4T), once thought to be contraindicated in combination because of their overlapping peripheral neuropathy toxicity, have proven well tolerated and effective. Combination therapy can increase antiviral suppression, prevent drug resistance, optimize drug exposure and simplify dosing, but it can also result in pharmacologic antagonism, subtherapeutic drug concentrations and unexpected toxicities. Clinical studies have confirmed in vitro studies showing pharmacologic antagonism for the combination of ZDV and d4T. Combining protease inhibitors with each other or with non-nucleoside reverse transcriptase inhibitors is complicated by effects both classes of drugs have on drug metabolism and clearance. These observations underline the importance of carefully conducted clinical studies to characterize safety, pharmacokinetics and efficacy of combination therapies. In this review, we will first summarize the clinical profile of new drugs which either became commercially available last year [nelfinavir, **nevirapine, delavirdine (DLV)**] or are in the late stages of clinical development (DMP-266, abacavir and 141W94). Later we will summarize new data on nucleoside, protease inhibitor and non-nucleoside reverse transcriptase combination regimens. Finally, we will briefly mention new drugs in early stages of development.

L8 ANSWER 22 OF 29 MEDLINE
1999054853 Document Number: 99054853. PubMed ID: 9835502. Patterns of resistance and cross-resistance to human immunodeficiency virus type 1 reverse transcriptase inhibitors in patients treated with the nonnucleoside reverse transcriptase inhibitor loviride. Miller V; de Bethune M P; Kober A; Sturmer M; Hertogs K; Pauwels R; Stoffels P; Staszewski S. (Zentrum der Inneren Medizin, J. W. Goethe Universitat, Frankfurt, Germany.. miller@em.uni-frankfurt.de) . **ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998 Dec) 42 (12) 3123-9.** Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) strains resistant to nonnucleoside reverse transcriptase inhibitors (NNRTIs) may easily be selected for in vitro and in vivo under a suboptimal therapy regimen. Although cross-resistance is extensive within this class of compounds, newer NNRTIs were reported to retain activity against laboratory strains containing defined resistance-associated mutations. We have characterized HIV -1 resistance to loviride and the extent of cross-resistance to **nevirapine, delavirdine, efavirenz**, HBY-097, and tivirapine in a set of 24 clinical samples from patients treated with long-term loviride monotherapy by using a recombinant virus assay. Genotypic changes associated with

resistance were analyzed by population sequencing. Overall, phenotypic resistance to loviride ranged from 0.04 to 3.47 log10-fold. Resistance was observed in samples from patients who had discontinued loviride for up to 27 months. Cross-resistance to the other compounds was extensive; however, fold resistance to efavirenz was significantly lower than fold resistance to nevirapine. No genotypic changes were detected in three samples; these were sensitive to all of the NNRTIs tested. The most common genotypic change was the K103N substitution. The range of phenotypic resistance in samples containing the K103N substitution could not be predicted from a genotypic analysis of known NNRTI resistance-associated mutations. The Y181C substitution was detected in one isolate which was resistant to loviride and delavirdine but sensitive to efavirenz, HBY-097, and tivirapine. Our data indicate that the available newer NNRTIs which retain activity against some HIV-1 strains selected by other compounds of this class in vitro may have compromised clinical efficacy in some patients pretreated with NNRTI.

L8 ANSWER 21 OF 29 MEDLINE
1999392739 Document Number: 99392739. PubMed ID: 10465070. Activity of non-nucleoside reverse transcriptase inhibitors against HIV-2 and SIV. Witvrouw M; Pannecouque C; Van Laethem K; Desmyter J; De Clercq E; Vandamme A M. (Rega Institute for Medical Research, Leuven, Belgium.) AIDS, (1999 Aug 20) 13 (12) 1477-83. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: After the initial discovery of 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine (HEPT) and tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one and thione (TIBO) derivatives, several other non-nucleoside reverse transcriptase (RT) inhibitors (NNRTI), including nevirapine (BI-RG-587), pyridinone derivatives (L-696,229 and L-697,661), delavirdine (U-90152), alpha-anilinophenylacetamides (alpha-APA) and various other classes of NNRTI have been described. The hallmark of NNRTI has been based on their ability to interact with a specific site ('pocket') of HIV-1 RT. OBJECTIVE: To investigate whether, in addition to HIV-1, different strains of HIV-2 (ROD and EHO) and SIV (mac251, agm3 and mndGB1) are sensitive to a selection of NNRTI i.e. delavirdine, the HEPT derivative I-EBU (MKC-442), 8-chloro-TIBO (tivirapine), alpha-APA (loviride), nevirapine and the pyridinone derivative L-697,661. METHODS AND RESULTS: The NNRTI tested inhibited the replication of the different strains of HIV -2 and SIV at micromolar concentrations. The inhibitory effects of the NNRTI on HIV-2-induced cytopathicity correlated well with their inhibitory effects on HIV-2 RT activity. Drug-resistant HIV-2 (EHO) variants containing the Ser102Leu and/or Glu219Asp mutations in their RT were selected after passaging the virus in MT-4 cells in the presence of increasing concentrations of delavirdine. The EHO virus mutants were at least 20-fold less susceptible to the antiviral effects of delavirdine. Some cross-resistance, depending on the mutant strain, was observed with the other NNRTI tested (i.e. MKC-442, tivirapine, loviride and pyridinone L-697,661). CONCLUSIONS: Our data demonstrate that NNRTI are not exclusively specific for HIV-1 but are also inhibitory to different HIV-2 and SIV strains. These observations will have important implications for the development of new NNRTI with higher activity against both HIV-1 and HIV-2.

Furthermore, in view of their anti-SIV activity, NNRTI could be evaluated further for their in vivo anti-retrovirus efficacy in non-human primate models.

L8 ANSWER 19 OF 29 MEDLINE
2000087919 Document Number: 20087919. PubMed ID: 10622039. Efavirenz: resistance and cross-resistance. Clotet B. (Hospital Universitari Germans Trias I Pujol, Badalona, Spain.) INTERNATIONAL JOURNAL OF CLINICAL PRACTICE. SUPPLEMENT, (1999 Jun) 103 21-5. Ref: 12. Journal code: 9712380. ISSN: 1368-504X. Pub. country: ENGLAND: United Kingdom. Language: English.

AB Resistant strains, the major cause of treatment failure in the management of HIV infection, evolve whenever virus replication is incompletely suppressed by drug therapy. In such cases, genotypic analysis of proviral DNA or phenotypic analysis of viral isolates or recombinant molecular clones can provide useful information for the clinician. With regard to NNRTIs, a single mutation at K103N is the most predominant resistance RT mutation observed with the NNRTIs and confers cross-resistance between efavirenz, nevirapine and delavirdine. K103N is found in HIV strains isolated from patients experiencing a viral rebound in plasma HIV-RNA levels who have received an efavirenz-containing regimen. Phenotypic analysis showed that the K103N mutation alone confers an approximate 20-fold increase in the IC50 of efavirenz.

L8 ANSWER 14 OF 29 MEDLINE
2001165888 Document Number: 21165698. PubMed ID: 11264999. International perspectives on antiretroviral resistance. Nonnucleoside reverse transcriptase inhibitor resistance. Deeks S G. (San Francisco General Hospital, San Francisco, California and University of California, San Francisco, California, USA.. sdeeks@php.ucsf.edu) . JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (2001 Mar 1) 26 Suppl 1 S25-33. Ref: 36. Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB Although understanding of nonnucleoside reverse transcriptase inhibitor (NNRTI) resistance is less clearly established than that of other classes of antiretroviral drugs, certain facts have been established. The treatment-associated genetic mutation profiles of the available NNRTIs have been mapped, and resistance has been found to develop rapidly after initiation of NNRTI therapy. Despite the chemical diversity of the NNRTIs, cross-resistance among agents of this class is nearly universal. Although the viral replicative capacity ("fitness") of NNRTI-induced viral variants has not been extensively studied, available data suggest that NNRTI-selected mutations confer little damage to viral fitness, and thus a single point mutation produces a strain that is both resistant and fit. Furthermore, with continued therapy, viral evolution persists, creating species with greater numbers of mutations and higher level phenotypic resistance. Taken together, these facts suggest that continued use of NNRTIs after emergence of resistance will produce variants of complex mutational patterns that limit future treatment options, and, therefore, strong consideration should be given to discontinuing NNRTIs after virologic failure is confirmed. This article describes the scientific literature establishing the efficacy and limitations of NNRTI therapy and attempts to define a role for this class of drug in the long-term

treatment of HIV-1 disease.

L8 ANSWER 12 OF 29 MEDLINE
2001239475 Document Number: 21232476. PubMed ID: 11333879. Genotypic correlates of phenotypic resistance to efavirenz in virus isolates from patients failing nonnucleoside reverse transcriptase inhibitor therapy. Bacheler L; Jeffrey S; Hanna G; D'Aquila R; Wallace L; Logue K; Cordova B; Hertogs K; Larder B; Buckery R; Baker D; Gallagher K; Scarnati H; Tritch R; Rizzo C. (DuPont Pharmaceuticals Company, Wilmington, Delaware 19880-0336, USA.. lee.bacheler@dupontpharma.com) . JOURNAL OF VIROLOGY, (2001 Jun) 75 (11) 4999-5008. Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Efavirenz (also known as DMP 266 or SUSTIVA) is a potent nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT) activity and of HIV-1 replication in vitro and in vivo. Most patients on efavirenz-containing regimens have sustained antiviral responses; however, rebounds in plasma viral load have been observed in some patients in association with the emergence of mutant strains of HIV-1. Virus isolates from the peripheral blood mononuclear cells (PBMCs) of patients with such treatment failures, as well as recombinant viruses incorporating viral sequences derived from patient plasma, show reduced in vitro susceptibility to efavirenz in association with mutations in the RT gene encoding K103N, Y188L, or G190S/E substitutions. Patterns of RT gene mutations and in vitro susceptibility were similar in plasma virus and in viruses isolated from PBMCs. Variant strains of HIV-1 constructed by site-directed mutagenesis confirmed the role of K103N, G190S, and Y188L substitutions in reduced susceptibility to efavirenz. Further, certain secondary mutations (V106I, V108I, Y181C, Y188H, P225H, and F227L) conferred little resistance to efavirenz as single mutations but enhanced the level of resistance of viruses carrying these mutations in combination with K103N or Y188L. Viruses with K103N or Y188L mutations, regardless of the initial selecting nonnucleoside RT inhibitor (NNRTI), exhibited cross-resistance to all of the presently available NNRTIs (efavirenz, nevirapine, and delavirdine). Some virus isolates from nevirapine or delavirdine treatment failures that lacked K103N or Y188L mutations remained susceptible to efavirenz in vitro, although the clinical significance of this finding is presently unclear.

L9 ANSWER 38 OF 38 MEDLINE
96161265 Document Number: 96161265. PubMed ID: 8592986. L-743, 726 (DMP-266): a novel, highly potent nonnucleoside inhibitor of the human immunodeficiency virus type 1 reverse transcriptase. Young S D; Britcher S F; Tran L O; Payne L S; Lumma W C; Lyle T A; Huff J R; Anderson P S; Olsen D B; Carroll S S; +. (Department of Medicinal Chemistry, Merck Research Laboratories, West Point, Pennsylvania 19486, USA.) ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1995 Dec) 39 (12) 2602-5. Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB The clinical benefit of the human immunodeficiency virus type 1 (HIV-1) nonnucleoside reverse transcriptase (RT) inhibitors (NNRTIs) is limited by the rapid selection of inhibitor-resistant viral variants. However, it may be possible to enhance the clinical utility of this inhibitor class by deriving compounds that express both high levels

of antiviral activity and an augmented pharmacokinetic profile. Accordingly, we developed a new class of NNRTIs, the 1, 4-dihydro-2H-3, 1-benzoxazin-2-ones. L-743, 726 (DMP-266), a member of this class, was chosen for clinical evaluation because of its in vitro properties. The compound was a potent inhibitor of the wild-type HIV-1 RT (Ki = 2.93 nM) and exhibited a 95% inhibitory concentration of 1.5 nM for the inhibition of HIV-1 replicative spread in cell culture. In addition, L-7743, 7726 was found to be capable of inhibiting, with 95% inhibitory concentrations of < or = 1.5 microM, a panel of NNRTI-resistant mutant viruses, each of which expressed a single RT amino acid substitution. Derivation of virus with notably reduced susceptibility to the inhibitor required prolonged cell culture selection and was mediated by a combination of at least two RT amino acid substitutions. Studies of L-743, 726 in rats, monkeys, and a chimpanzee demonstrated the compound's potential for good oral bioavailability and pharmacokinetics in humans.

L9 ANSWER 37 OF 38 MEDLINE
1999054853 Document Number: 99054853. PubMed ID: 9835502. Patterns of resistance and cross-resistance to human immunodeficiency virus type 1 reverse transcriptase inhibitors in patients treated with the nonnucleoside reverse transcriptase inhibitor loviride. Miller V; de Bethune M P; Kober A; Sturmer M; Hertogs K; Pauwels R; Stoffels P; Staszewski S. (Zentrum der Inneren Medizin, J. W. Goethe Universitat, Frankfurt, Germany.. miller@em.uni-frankfurt.de) . ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (1998 Dec) 42 (12) 3123-9. Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB Human immunodeficiency virus type 1 (HIV-1) strains resistant to nonnucleoside reverse transcriptase inhibitors (NNRTIs) may easily be selected for in vitro and in vivo under a suboptimal therapy regimen. Although cross-resistance is extensive within this class of compounds, newer NNRTIs were reported to retain activity against laboratory strains containing defined resistance-associated mutations. We have characterized HIV -1 resistance to loviride and the extent of cross-resistance to nevirapine, delavirdine, efavirenz, HBY-097, and tivirapine in a set of 24 clinical samples from patients treated with long-term loviride monotherapy by using a recombinant virus assay. Genotypic changes associated with resistance were analyzed by population sequencing. Overall, phenotypic resistance to loviride ranged from 0.04 to 3.47 log10-fold. Resistance was observed in samples from patients who had discontinued loviride for up to 27 months. Cross-resistance to the other compounds was extensive; however, fold resistance to efavirenz was significantly lower than fold resistance to nevirapine. No genotypic changes were detected in three samples; these were sensitive to all of the NNRTIs tested. The most common genotypic change was the K103N substitution. The range of phenotypic resistance in samples containing the K103N substitution could not be predicted from a genotypic analysis of known NNRTI resistance -associated mutations. The Y181C substitution was detected in one isolate which was resistant to loviride and delavirdine but sensitive to efavirenz, HBY-097, and tivirapine. Our data indicate that the available newer NNRTIs which retain activity against some HIV-1 strains selected by other compounds of this class in vitro may have compromised clinical efficacy in some patients pretreated with

NNRTI.

L9 ANSWER 35 OF 38 MEDLINE
2000170570 Document Number: 20170570. PubMed ID: 10708276. Non-nucleoside reverse transcriptase inhibitor resistance among patients failing a nevirapine plus protease inhibitor-containing regimen. Casado J L; Hertogs K; Ruiz L; Dronda F; Van Cauwenberge A; Arno A; Garcia-Arata I; Bloor S; Bonjoch A; Blazquez J; Clotet B; Larder B. (Infectious Diseases Unit, Ramon y Cajal Hospital, Madrid, Spain.. jcasado@hrc.insalud.es) . AIDS, (2000 Jan 28) 14 (2) F1-7. Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB OBJECTIVE: To determine the rate of nevirapine resistance in patients failing a nevirapine plus protease inhibitor (PI)-based regimen, and whether these isolates remain susceptible to other non-nucleoside reverse transcriptase inhibitors (NNRTI). DESIGN AND SETTING: A retrospective cohort study in two tertiary university hospitals. PATIENTS: Eighty-eight HIV-infected, NNRTI-naive patients receiving nevirapine plus PI as a rescue regimen after PI treatment failure. MAIN OUTCOME MEASURES: Genotypic and phenotypic resistance data at inclusion (73 and 60 plasma samples, respectively) and after 24 weeks (53 and 42 samples). RESULTS: Baseline phenotypic susceptibility to nevirapine was found in 70% of patients, and similar data were observed for efavirenz (91%) and delavirdine (71%). NNRTI resistance-associated mutations were found in 11 patients (12.5%). At 24 weeks, resistant isolates to nevirapine were found in 92% of patients, and correlated with similar resistance to efavirenz (68%) and delavirdine (73%). In the genotypic analysis, the Y181 C mutation was observed in 76% of mutants, and the most common changes were a combination of mutations at positions Y181C/K103N (23%) and the single mutation Y181C (15%). The development of nevirapine resistance was associated with baseline resistance to PI included in the regimen (P= 0.01). For isolates containing the single amino acid substitution Y181C, 29% remained fully susceptible to efavirenz, whereas 14% showed intermediate resistance to efavirenz and delavirdine. CONCLUSION: The failure of a nevirapine plus PI-containing regimen is associated with nevirapine resistance in most patients, with the most common mutation occurring at amino acid residue 181. Although there is a high degree of cross-resistance among NNRTI, nearly one third of resistant isolates carrying the single Y181C mutation remain susceptible to efavirenz.

L9 ANSWER 31 OF 38 MEDLINE
2000461664 Document Number: 20408577. PubMed ID: 10952598. Human immunodeficiency virus type 1 mutations selected in patients failing efavirenz combination therapy. Bacheler L T; Anton E D; Kudish P; Baker D; Bunville J; Krakowski K; Bolling L; Aujay M; Wang X V; Ellis D; Becker M F; Lasut A L; George H J; Spalding D R; Hollis G; Abremski K. (DuPont Pharmaceuticals Company, Experimental Station, Wilmington, Delaware 19880-0336, USA.. lee.bacheler@dupontpharma.com) . **ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, (2000 Sep) 44 (9) 2475-84.** Journal code: 0315061. ISSN: 0066-4804. Pub. country: United States. Language: English.

AB **Efavirenz** is a potent and selective nonnucleoside inhibitor of human immunodeficiency virus type 1 (HIV-1) reverse transcriptase (RT). Nucleotide sequence analyses of the protease and RT genes

(coding region for amino acids 1 to 229) of multiple cloned HIV -1 genomes from virus found in the plasma of patients in phase II clinical studies of efavirenz combination therapy were undertaken in order to identify the spectrum of mutations in plasma-borne HIV -1 associated with virological treatment failure. A **K103N** substitution was the HIV-1 RT gene mutation most frequently observed among plasma samples from patients for whom combination therapy including efavirenz failed, occurring in at least 90% of cases of efavirenz-indinavir or efavirenz-zidovudine (ZDV)-lamivudine (3TC) treatment failure. **V108I and P225H** mutations were observed frequently, predominantly in viral genomes that also contained other nonnucleoside RT inhibitor (NNRTI) resistance mutations. **L100I, K101E, K101Q, Y188H, Y188L, G190S, G190A, and G190E** mutations were also observed. **V106A, Y181C, and Y188C** mutations, which have been associated with high levels of resistance to other NNRTIs, were rare in the patient samples in this study, both before and after exposure to efavirenz . The spectrum of mutations observed in cases of virological treatment failure was similar for patients initially dosed with efavirenz at 200, 400, or 600 mg once a day and for patients treated with efavirenz in combination with indinavir, stavudine, or ZDV-3TC. The proportion of patients carrying NNRTI resistance mutations, usually K103N, increased dramatically at the time of initial viral load rebound in cases of treatment failure after exposure to efavirenz. Viruses with multiple, linked NNRTI mutations, especially **K103N-V108I and K103N-P225H** double mutants , accumulated more slowly following the emergence of K103N mutant viruses.

L13 ANSWER 4 OF 6 MEDLINE

1998001335 Document Number: 98001335. PubMed ID: 9343170. Characteristics of the Pro225His mutation in human immunodeficiency virus type 1 (HIV-1) reverse transcriptase that appears under selective pressure of dose-escalating quinoxaline treatment of HIV-1. Pelemans H; Esnouf R; Dunkler A; Parniak M A; Vandamme A M; Karlsson A; De Clercq E; Kleim J P; Balzarini J. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) **JOURNAL OF VIROLOGY, (1997 Nov) 71 (11) 8195-203.** Journal code: 0113724. ISSN: 0022-538X. Pub. country: United States. Language: English.

AB Treatment of human immunodeficiency virus type 1 (HIV-1)-infected CEM cell cultures with escalating concentrations of the quinoxaline S-2720 resulted in an ordered appearance of single and multiple mutant virus strains that gradually became resistant to the quinoxaline and other nonnucleoside reverse transcriptase (RT) inhibitors (**NNRTIs**). A novel mutation, **Pro225His**, consistently appeared in a Val106Ala RT-mutated genetic background. The contribution of this mutation to the resistance of the mutant HIV-1 RT to NNRTIs was additive to the resistance caused by the Val106Ala mutation. Interestingly, site-directed mutagenesis studies revealed that the **Pro225His**-mutated RT had acquired markedly greater sensitivity to bis(heteroaryl)piperazine (BHAP U-90152) (**delavirdine**) but not to any of the other NNRTIs. The kinetics of inhibition of the Pro225His mutant RT by the NNRTIs (including BHAP U-90152) was not substantially different from that observed for the wild-type RT. The hypersensitivity of the mutant enzyme and virus to BHAP U-90152 could be rationally explained by the molecular-structural determinants of the RT-BHAP complex, which has recently been resolved by X-ray crystallography.

L15 ANSWER 8 OF 9 MEDLINE

96249959 Document Number: 96249959. PubMed ID: 8656777. Non-nucleoside reverse transcriptase inhibitors (NNRTIs) for the treatment of human immunodeficiency virus type 1 (HIV-1) infections: strategies to overcome drug resistance development. de Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) MEDICINAL RESEARCH REVIEWS, (1996 Mar) 16 (2) 125-57. Ref: 180. Journal code: 8103150. ISSN: 0198-6325. Pub. country: United States. Language: English.

L17 ANSWER 9 OF 9 MEDLINE
94137263 Document Number: 94137263. PubMed ID: 7508227. HIV resistance to reverse transcriptase inhibitors. De Clercq E. (Rega Institute for Medical Research, Katholieke Universiteit Leuven, Belgium.) BIOCHEMICAL PHARMACOLOGY, (1994 Jan 20) 47 (2) 155-69. Ref: 119. Journal code: 0101032. ISSN: 0006-2952. Pub. country: ENGLAND: United Kingdom. Language: English.

L18 ANSWER 5 OF 6 MEDLINE
1999208030 Document Number: 99208030. PubMed ID: 10193687. Managing resistance to anti-HIV drugs: an important consideration for effective disease management. Vandamme A M; Van Laethem K; De Clercq E. (Rega Institute for Medical Research and University Hospitals, Katholieke Universiteit Leuven, Belgium.. annemie.vandamme@uz.kuleuven.ac.be) . DRUGS, (1999 Mar) 57 (3) 337-61. Ref: 214. Journal code: 7600076. ISSN: 0012-6667. Pub. country: New Zealand. Language: English.

AB Current recommendations for the treatment of HIV-infected patients advise highly active antiretroviral therapy (HAART) consisting of combinations of 3 or more drugs to provide long-term clinical benefit. This is because only a complete suppression of virus replication will be able to prevent virus drug resistance, the main cause of drug failure. Virus drug resistance may remain a cause of concern in patients who have already received suboptimal mono- or bitherapy, or for patients who do not experience complete shut-down of virus replication under HAART. For these patients, replacement of one combination therapy regimen by another at drug failure, taking into account the existing resistance profile, will be needed. The development of new drugs will remain necessary for those patients who have failed to respond to all currently available drugs, as will be the institution of more effective and less toxic HAART regimens.

L18 ANSWER 1 OF 6 MEDLINE
2000300543 Document Number: 20300543. PubMed ID: 10843523. Phenotypic assays and sequencing are less sensitive than point mutation assays for detection of resistance in mixed HIV-1 genotypic populations. Van Laethem K; Van Vaerenbergh K; Schmit J C; Sprecher S; Hermans P; De Vroey V; Schuurman R; Harrer T; Witvrouw M; Van Wijngaerden E; Stuyver L; Van Ranst M; Desmyter J; De Clercq E; Vandamme A M. (Rega Institute for Medical Research and University Hospitals, Leuven, Belgium.) **JOURNAL OF ACQUIRED IMMUNE DEFICIENCY SYNDROMES, (1999 Oct 1) 22 (2) 107-18.** Journal code: 100892005. ISSN: 1525-4135. Pub. country: United States. Language: English.

AB The sensitivity and discriminatory power of the 151 and 215 amplification refractory mutation system (ARMS) were evaluated, and their performance for the detection of drug resistance in mixed genotypic populations of the reverse transcription (RT) gene of HIV-1 were compared with T7 sequencing, cycle sequencing, the line probe assay (LiPA) HIV-1 RT test, and the recombinant virus assay (RVA). ARMS and the LiPA HIV-1 RT test were shown to be

able to detect minor variants that in particular cases comprised only 1%. T7 sequencing on an ALF semiautomated sequencer could correctly score mixtures only when variants were present at 50%. Cycle sequencing on an ABI PRISM 310 improved the sensitivity for mixtures to about 25%. Using RVA, it was shown that at least 50% of the virus population needed to carry the resistance mutation at codon 184 to afford phenotypic resistance against lamivudine. The two point mutation assays therefore proved to be more sensitive methods than sequencing and RVA to reliably determine a gradual shift in HIV-1 drug resistance
mutations in follow-up of patients infected with HIV-1. In 4 of 5 treated patients who were followed by ARMS, a gradual shift in resistant genotypic populations was observed during a period of 6 to 19 months. For 1 patient, a shift from wild to mutant type at position 151 occurred within 2 months, without mixed genotypic intermediate type's being detected.

L18 ANSWER 3 OF 6 MEDLINE
1999392739 Document Number: 99392739. PubMed ID: 10465070. Activity of non-nucleoside reverse transcriptase inhibitors against HIV-2 and SIV. Witvrouw M; Pannecouque C; Van Laethem K; Desmyter J; De Clercq E; Vandamme A M. (Rega Institute for Medical Research, Leuven, Belgium.) **AIDS, (1999 Aug 20) 13 (12) 1477-83.** Journal code: 8710219. ISSN: 0269-9370. Pub. country: ENGLAND: United Kingdom. Language: English.

AB BACKGROUND: After the initial discovery of 1-(2-hydroxyethoxymethyl)-6-(phenylthio)thymine (HEPT) and tetrahydroimidazo[4,5,1-jk][1,4]benzodiazepin-2(1H)-one and thione (TIBO) derivatives, several other non-nucleoside reverse transcriptase (RT) inhibitors (NNRTI), including nevirapine (BI-RG-587), pyridinone derivatives (L-696,229 and L-697,661), delavirdine (U-90152), alpha-anilinophenylacetamides (alpha-APA) and various other classes of NNRTI have been described. The hallmark of NNRTI has been based on their ability to interact with a specific site ('pocket') of HIV-1 RT. OBJECTIVE: To investigate whether, in addition to HIV-1, different strains of HIV -2 (ROD and EHO) and SIV (mac251, agm3 and mndGB1) are sensitive to a selection of NNRTI i.e. delavirdine, the HEPT derivative I-EBU (MKC-442), 8-chloro-TIBO (tivirapine), alpha-APA (loviride), nevirapine and the pyridinone derivative L-697,661. METHODS AND RESULTS: The NNRTI tested inhibited the replication of the different strains of HIV-2 and SIV at micromolar concentrations. The inhibitory effects of the NNRTI on HIV-2-induced cytopathicity correlated well with their inhibitory effects on HIV-2 RT activity. Drug-resistant
HIV-2 (EHO) variants containing the Ser102Leu and/or Glu219Asp mutations in their RT were selected after passaging the virus in MT-4 cells in the presence of increasing concentrations of delavirdine. The EHO virus mutants were at least 20-fold less susceptible to the antiviral effects of delavirdine. Some cross-resistance, depending on the mutant strain, was observed with the other NNRTI tested (i.e. MKC-442, tivirapine, loviride and pyridinone L-697,661). CONCLUSIONS: Our data demonstrate that NNRTI are not exclusively specific for HIV-1 but are also inhibitory to different HIV-2 and SIV strains. These observations will have important implications for the development of new NNRTI with higher activity against both HIV-1 and HIV-2. Furthermore, in view of their anti-SIV activity, NNRTI could be evaluated further for their in vivo anti-retrovirus efficacy in non-human primate models.